Remarks

Upon entry of the amendment, claims 24-36, 39-43, 46-50, 53-57, 60-73 will be pending. Claims 36, 43, 50, 57, 64, and 69 have been amended. Support for the amended claims is found throughout the specification as filed. More specifically, support can be found at page 58, lines 16-18. Thus, no new matter has been introduced.

Claims Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 25 and 31 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. *See,* Paper No.17, page 2, second paragraph. More particularly, the Examiner alleges that the written description requirement is to be applied as "requiring specific Methionine lacking as amino acid residue 1 specifically regarding the claimed SEQ ID NO: 73 which was not disclosed specifically as filed[.]" *See*, Paper No. 17, page 2, second paragraph.

Applicants respectfully disagree and traverse.

In the M.P.E.P's "Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, para. 1 'Written Description' Requirement" section, it is stated,

> Such a review [of the disclosure] is conducted from the standpoint of one of skill in the art at the time the application was filed (see, e.g., *Wang Labs. V. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written disclosure requirement. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

See, M.P.E.P. 2163 II. A.2., at 2100-160.

Therefore, the written description of the invention relies heavily on the knowledge of one of skill in the art. Further, the claims should be read in light of the specification as a whole. Applicants respectfully submit that one of skill in the art (for instance, a Ph.D. in molecular biology) reading the entire specification and then reviewing claims 25 and 31 would easily and reasonably conclude that Applicants had possession of a polypeptide of amino acid sequence SEQ ID NO: 73 without its initial Methionine. The statement regarding the post-translational

modifications of the polypeptides given by Applicants on pages 150-151 applies to all the "polypeptides of the invention," of which SEQ ID NO: 73 is an embodiment. *See*, specification page 150, line 31. Applicants' disclosure on page 151, lines 3-6, states that the modification, including the removal, of the N-terminal Methionine residue depends not only on the host type (eukaryotic or prokaryotic) but also on the residues close to the initial Methionine. The specification envisions several expression systems, both eukaryotic and prokaryotic, *see*, specification page 151, line 7, to page 152, line 27, and the pre- and post-translational modifications naturally occurring in such systems. *See*, specification, page 153, lines 13-28. Therefore, Applicants' statement that "the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells, " envisions polypeptides, produced according to the teachings of the specification, which may not have a N-terminal Methionine residue. *See*, specification, page 151, lines 1-3.

Furthermore, Applicants disclose at page 72, second row, of the specification that the polypeptide presently claimed, SEQ ID NO: 73, comprises 105 amino acid residues. The amino acid sequence given in the sequence listing for SEQ ID NO: 73 indicates that its first amino acid residue is a Methionine residue. Therefore, based on the teachings of the specification, which indicate that the initial Methionine residue of polypeptides produced using any one of the methods described is removed after translation, one of skill in the art would be readily able to envision the amino acid sequence comprising residues 2 to 105 of SEQ ID NO: 73, and the amino acid sequence encoded by the HATCM08 cDNA contained in the ATCC Deposit No. 203858, excepting the N-terminal Methionine residue, as claimed. Therefore, based on the specification and the knowledge of one skilled in the art, Applicants assert that one of ordinary skill in the art would reasonably conclude that Applicants had possession of the claimed invention.

The Examiner further asserts that such an "argument is moot in that it is not directed to the basis of the rejection which is the lack of written description and not what could reasonably be concluded." *See*, Paper No. 17, page 3, lines 11-13 (emphasis added). Applicants respectfully disagree and traverse.

Applicants respectfully point to the M.P.E.P., which states:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed

> invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 116."

See, M.P.E.P. 2163 I. at 2100-155 (emphasis added).

Applicants assert that, indeed, the determination as to whether the disclosure satisfies the written description requirement is based on what could reasonably be concluded by one of skill in the art. The Federal Circuit emphasized the importance of what the person of skill in the art would understand from reading the specification, rather than whether the specific embodiments had been explicitly described or exemplified. Indeed, as the court noted, "the issue is whether one of skill in the art could derive the claimed ranges from the patent's disclosure." *Unocal*, 208 F.3d at 1001 (Fed. Cir. 2000) (emphasis added).

Applicants further understand the pending rejection of claims 25 and 31 under 35 U.S.C. 112, para. 1, as written by the Examiner, as being based on an alleged lack of literal description of an amino acid sequence comprising residues 2 to 105 of SEQ ID NO: 73. Applicants assert that such a literal description is not required to fulfill the written description requirement, as it is stated in the M.P.E.P. that "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." *See*, M.P.E.P. 2163.02 at 2100-167. It is further stated:

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

See, M.P.E.P. 2163.3.a on page 2100-162. Rather, the M.P.E.P. indicates that, in order "[t]o comply with the written description requirement of 35 U.S.C. 112, para. 1... each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure." *See*, M.P.E.P., 2163 II. A. 3. b) at 2100-165. Applicants respectfully submit that the standard articulated above by the Examiner for satisfying the written description requirement is not one espoused by the courts or by the U.S.P.T.O.

In an analysis of written description under 35 U.S.C. § 112, first paragraph, the Examiner bears the initial burden of presenting a *prima facie* case of unpatentability. This burden is only discharged if the Examiner can present evidence or reasons why one skilled in the art would not reasonably conclude that Applicants possessed the subject matter as of the priority date of the present application. *See, In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q.2d 90, 96 (C.C.P.A. 1976); M.P.E.P. § 2163.04. In the instant case, Applicants respectfully reiterate that the Examiner has not met this burden. In the present Office Action, the Examiner asserts

> [T]he lack of written basis for the Methionine lack in SEQ ID NO: 73 has been set forth as clear evidence or reasons and thus this argument is moot, including the acknowledgment that applicants have not pointed to such Methionine missing SEQ ID NO: 73 specifically as filed.

See, Paper No. 17, page 3, lines 5-8.

Applicants respectfully disagree and traverse.

Applicants assert that the specification, including the original claims as filed, provides ample disclosure of the amino acid sequence of SEQ ID NO: 73, of several heterologous expression systems which can be used to produce the polypeptides of the invention, and of the post-translational modifications of such polypeptides, including removal of the initial Methionine residue. *See*, specification, pages 148-161. Applicants assert that one of ordinary skill in the art would reasonably conclude that one of the many contemplated polypeptides of the invention is indeed SEQ ID NO: 73 lacking its initial Methionine residue.

Thus, one of ordinary skill in the art would conclude that Applicants, at the time of the invention, were in possession of the claimed polypeptides. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 25, and 31 under 35 U.S.C. § 112, first paragraph.

Claims Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 25-27, 31-33, 36, 39-43, 46-50, 53-57, and 60-73 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. *See,* Paper No.17, page 4. More specifically, the Examiner states at page 4, third paragraph:

> [S]ince the claimed invention is only supported as to usage regarding a polypeptide consisting only of the entirety of SEQ ID NO: 73, one skilled in the art would not know how to use the claimed invention directed to fragments thereof.

Applicants respectfully disagree.

Applicants have amended independent claims 24, 30, 36, 43, 50, 57, 64, and 69 to add a functional limitation to the pending claim. Namely, the added limitation is that the claimed polypeptides of the invention be expressed in adrenal gland tumors. Support for these amendments can be found in the specification at page 58, lines 16-18.

Applicants respectfully submit that the legal standard for evaluating enablement, as cast by the C.C.P.A. and the Federal Circuit, is not whether the specification discloses any or all alterations that can be made in the claimed proteins that will not alter the functional activity of the proteins, but rather whether proteins encompassed by the claims have at least a single use, and this use can be confirmed, without undue experimentation, by following procedures either described in the specification or otherwise known in the art. *See, In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976):

> To require such a complete disclosure would apparently necessitate a patent with "thousands of examples . . . More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments . . . .

This holding was confirmed by the Federal Circuit. As Judge Rich explained in *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1445 (Fed.Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility" (emphasis provided). According to M.P.E.P. § 2164.01(b), "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied." *Citing In re Fisher*, 427 F2d 833,839 166 USPQ 18, 24 (CCPA 1970).

Thus, Applicants submit that to be fully enabled, the present specification need only teach the skilled artisan to be able to, for example, detect the claimed proteins, or protein fragments, or fusion proteins, in specific tissues. Polypeptide fragments are taught in the specification at, *e.g.*, page 99, line 26 to page 100, line 25, and uses for these fragments are also taught in the specification at, *e.g.*, page 101, lines 1-10. Specifically, those fragments can have the ability to form multimers with polypeptides of the invention, or have the ability to bind to a receptor or ligand for a polypeptide of the invention. Antibodies can be then generated against those fragments and, in turn, be used to detect the polypeptides of the invention in biological samples. Methods to generate antibodies are described in the specification at, *e.g.*, page 111, line 5 to page 116, line 10, and are well known in the art. Furthermore, methods to use the

antibodies generated against fragments of polypeptides of the invention are described in the specification at, *e.g.*, page 128, line 27 to page 133, line 5. Additionally, conjugate or fusion proteins are taught in the specification at, for instance, page 107, line 22; page 110, line 19; page 147, line 4 to page 148, line 30; page 152, lines 7-11; page 157, line 7 to page 161, line 2; and Example 9, page 296.

As far as determining whether experimentation is undue, the factors that can be considered have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine.

Applicants have adequately provided the starting materials and guidance to one skilled in the art to make, test, and use the claimed polypeptides. For example, the specification explicitly teaches many structural and functional components of the claimed Secreted Protein HATCM08 such as the full-length polypeptide sequence and the secreted portion of Secreted Protein HATCM08 (*see*, e.g., Table 1, row 23, columns 5 and 11-15; and pages 88-90 of the specification; SEQ ID NO: 33 (the cDNA sequence which encodes the claimed polypeptides); SEQ ID NO: 73 (the full-length polypeptide sequence of Secreted Protein HATCM08)); preferred polypeptide fragments of Secreted Protein HATCM08 (*see, e.g.,* page 57, lines 20-31); antigenic epitopes of Secreted Protein HATCM08 (*see, e.g.*, page 58, line 31 to page 59, line 2; and page 102, line 26 to page 104, line 5); and secondary structural features of the HATCM08 protein including alpha, beta, turn and coil regions, hydrophilicity and hydrophobicity, amphipathic regions, flexible regions, and surface probability (*see, e.g.,* page 100, lines 17-25). These disclosed structural and functional components of the claimed Secreted Protein HATCM08 would be useful, for example, in predicting which amino acid substitutions would be likely to maintain the structural conformation and electrochemical properties of the protein, which substitutions would likely result in "silent" mutations, and which substitutions would likely affect the antigenicity of the polypeptide. By choosing alterations that maintain or alter certain structures, the desired activity of the claimed protein can be achieved. Importantly, based on these teachings, the skilled artisan would not have to simply rely on trial and error to make and use the invention.

In addition, Applicants respectfully point out that methods were available as of the priority date of the instant application for readily making and identifying numerous altered

proteins that retain functions of the original protein (*see*, for example, page 75, lines 4-12 and page 90 lines 18 to page 97, line 31 of the specification).

Applicants submit that it would be routine for one of ordinary skill in the art to make and use an antibody which specifically binds to SEQ ID NO: 73, a fragment of SEQ ID NO: 73, a fusion protein containing SEQ ID NO: 73, or a polypeptide which shares 90% or more sequence identity with SEQ ID NO: 73.

Applicants submit that because of: (1) the availability of routine methods for generating antibodies, (2) the availability of routine techniques for detecting the presence of specific proteins; (3) the knowledge of the amino acid sequence constituting SEQ ID NO: 73; and (4) the high level of skill in the field of immunology and molecular biology, one skilled in the art could routinely generate the claimed antibodies and determine whether any given biological samples contained a polypeptide of the invention and satisfy the limitations recited in the claims.

In view of the above discussion, Applicants believe the Examiner's concerns have been fully addressed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 25-27, 31-33, 36, 39-43, 46-50, 53-57, and 60-73 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Claims Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 25-27, 31-33, 36, 39-43, 46-50, 53-57, and 60-73 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. *See,* Paper No. 17, page 6, first paragraph. More particularly, the Examiner alleges "[w]hile the instant specification provides a process for obtaining polypeptides with immunogenicity, there is no further information pertaining to polypeptide relevant structural or physical characteristics[.]" *See*, Paper No. 17, paragraph bridging pages 7-8.

Applicants respectfully disagree.

Applicants have amended independent claims 24, 30, 36, 43, 50, 57, 64, and 69 to add a functional limitation to the pending claim. Namely, the added limitation is that the claimed polypeptides of the invention be expressed in adrenal gland tumors. Support for this amendment may be found in the specification at page 58, lines 16-18.

Applicants assert that the current amendments provide the relevant physical characteristics the Examiner alleges is lacking. Applicants respectfully point out that neither the functional limitation, nor the claims as previously amended, requires one to know the immunogenicity of any particular residue within SEQ ID NO: 73. Furthermore, Applicants point the Examiner to their response, above, to the rejection of claims under 35 U.S.C. § 112, first paragraph, enablement for reference to parts of the specification where written support for the relevant structural characteristics of the claimed polypeptides of the invention can be found.

In view of the above discussion, Applicants believe the Examiner's concerns have been fully addressed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 25-27, 31-33, 36, 39-43, 46-50, 53-57, and 60-73 under 35 U.S.C. § 112, first paragraph, for lack of written description.

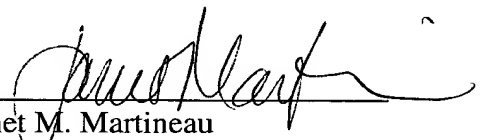
Conclusion

In view of the foregoing remarks, Applicants believe they have fully addressed the Examiner's concerns and that this application is now in condition for allowance. An early notice to that effect is urged. A request is made to the Examiner to call the undersigned at the phone number provided below if any further action by Applicants would expedite allowance of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: September 26, 2003

Respectfully submitted,

By 

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